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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,609	12/28/2000	David Robertson	1242/27/2/2	6747

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	13

DATE MAILED: 11/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,609	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6a .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' response to the office action and amendment (Paper No. 11) filed on May 30, 2003 has been entered.

2. The IDS (Paper No. 12) filed on May 30, 2003 has been entered and considered.

3. The Declaration submitted under37 C.F.R. 131 has been entered and considered.

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see at least page 97, line3). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in orthostatic intolerance, does not reasonably provide enablement for a method of screening for susceptibility to sub-optimal NE transport in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (see In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the invention:

The claims are drawn to a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in a subject. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Breadth of the claims:

Claim 1, is drawn to a method of screening for susceptibility to sub-optimal norepinephirne (NE) transport in a subject. Claim 2 is further limiting the claim 1 to orthostatic intolerance and claims 3, 6-7, 9-13, and 16-17 are drawn to the said method of claim 1, further limiting the method. Claims 4-5, 8, 14 are drawn to a method of screening for susceptibility to sub-optimal norepinephirne (NE) transport in a subject with a detection of polymorphism in NE transporter gene transmembrane domain of exon 9 comprising G to C transversion resulting a in a NE transporter encoding polypeptide having a proline at position 457.

Amount of Direction and Guidance

The specification discloses the identity of a specific C to G nucleotide change which result in an alanine to proline change in amino acid position 457 (A457P) in a proband having orthostatic intolerance (Fig. 2A-2B). The specification on page 9, asserts a comparison of this mutation to a wild type NE transporter (NET) correlation among the related murine and bovine and frog NET with that of human and further asserts the presence of this mutation in the proband having

orthostatic intoleranace and in the family members of the proband (Fig. 2C-2F). The specification teaches that the mutation (A457P) is correlated to NE transport and its presence in the orthostatic intolerance. The specification also discloses the identification of the position of the mutation to the G to C transversion at base 237 within exon 9.

Presence and Absence of working examples:

The specification discloses a method of identifying exon 9 mutation, that is A457P in a proband (having orthostatic intolerance), with allele specific oligonucleotides (SEQ ID Nos. 9 and 10). The specification also provides primer sets for amplification of other exons of human NET gene. The specification also provides a silent (c154a) and missense (g237c) mutations in exon 9, proband being heterozygous for both of theses mutations, wherein the missense mutation is correlated with coding alteration of alanine to proline (A457P) within a highly conserved region of transmembrane domain of exon 9 (Example 4). The examples 5-6 in the specification establish a positive correlation between the presence of the mutant allele (AP) and the abnormal clearance of NE in orthostatic intolerance. Although the specification asserts identification of additional single nucleotide polymorphisms in human NET gene, the specification does not demonstrate any correlation between the NE transport in general with any specific mutation except for the correlation of the mutation A457P in orthostatic intolerance. Thus the specific mutation was correlated with the NE transport in orthostatic intolerance and not with the general NE transport in a subject.

Level of Predictability and unpredictability in the art :

Predictability in the art suggests mutations in other exons of the NET gene, however no specific mutation is associated with any specific type of norepinephrine transport or a disease, for

example Stober et al. (Amer. J. Med. Genet., Vol. 67, pp. 523-532, 1996) teaches 13 DNA variants of NET gene, none of which is associated with any major psychiatric diseases. However, the art does not establish a predictable association that any specific mutation in NET is predictably associated with the broadly recited "sub-optimal NE transport" system. The art is further silent with regard to a predictable association between any specific mutation in NET and NE transport in general. The claims further broadly encompass screening for susceptibility to sub-optimal NE transport by detecting a polymorphism in NET gene. The specification, however does not establish a statistically significant association with any of the disclosed mutations in NET gene, with the susceptibility to sub-optimal NE transport (except for the A457P mutation in exon 9 in orthostatic intolerance), that would establish all mutations or polymorphisms result in the susceptibility to sub-optimal NE transport. Further, to date, no teaching is available in the art with regards to a universal correlation between any mutation in NET gene and an association with any general or specific susceptibility to NE transport. It is apparent from the prior art that the unpredictability is high and the instant specification fails to teach any particular mutation associated with the susceptibility to sub-optimal NE transport. Given the broad scope of the claims, the specification does not provide any specific example that would easily predict a significant association of a polymorphisim in NET gene with general susceptibility to sub-optimal NE transport. In addition, the specification does not establish the identity of all specific critical nucleotide or amino acid alteration(s) in NET gene that are associated with the susceptibility to the sub-optimal NE transport. Since the specification has not identified any polymorphism would result in susceptibility to sub-optimal NE transport, it is further unclear whether these mutations or any specific mutation will have a significant affect or not.

Level of Skill in the Art:

The level of skill in the art is deemed to be high.

Quantity of Experimentation Necessary:

It would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation that any mutation in NET gene is significantly associated with susceptibility to NE transport. To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different polymorphims, to determine if any general alteration or mutation in NET gene, was associated with general susceptibility to sub-optimal NE transport. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of the art.

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the presence of a working example which does not address the scope of the claim and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claim 1-3, 6-7, 13, and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacob et al. (Circulation, Vol. 99, pp. 1706-1712, 1999) in view of Jonnsson et al. (Psychiatry Research, Vol. 79, pp. 1-9, 1998).

Jacob et al. teach a method of claim 2, for screening for susceptibility to sub-optimal nor epinephrine (NE) transport in human subjects with orthostatic intolerance wherein Jacob et al. teach that the method comprises (a) obtaining a biological sample from the subject having orthostatic intolerance (see page 1707, column 1, paragraph 1); and detecting sup-optimal norepinephrine (comprises protein) in the biological samples (see page 1707, column 2, paragraphs 1-4, page 1708, column 2, paragraph 2) and associating the presence of abnormal NE transport to the susceptibility of a subject to orthostatic intolerance or sub-optimal NE clearance (see page 1710, column 1, paragraphs 1-2, column 2, paragraph 1, page 1711, column 2, paragraph 3). However, Jacob et al. did not teach polymorphisms in NE transporter gene.

Jonnsson et al. teach a method for screening for susceptibility to norepinephrine (NE) transport in a human subject wherein Jonnsson et al. teach that the method comprises (a) obtaining a biological sample from a human subject (see page 3, column 1, paragraph 1); and detecting a polymorphism of a norepinephrine (NE) transporter in the biological sample from the subject (see page 3, column 2, paragraph 3) and detecting the presence of the polymorphism as an indication of the susceptibility of the subject to a sub-optimal NE transport (see page 7, column 1, paragraph 2). Jonnsson et al. also teach that the method comprises (i) biological sample comprising nucleic acid (see page 3, column 1, paragraph 2); (ii) detection of polymorphism by amplifying the target nucleic acid using PCR (see page 3, column 2, paragraph 3); (iii) detecting the polymorphism using a reagent (oligonucleotide primers) (see page 3, column 2, paragraph 3); and human subjects (see page 3, column 1, paragraph 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method of detecting correlating or associating abnormal NE transport with orthostatic tolerace as taught by Jacob et al. with a method for detecting NE transporter gene polymorphisms as taught by Jonsson et al. to achieve expected advantage of developing a sensitive and improved method for detecting susceptibility of a subject to orthosatic intolerance (OI) because Jonsson et al. taught a possible association between NE transporter gene polymorphism and differential regulation of NE transport or turnover rate (see page 1, abstract). An ordinary practitioner would have been motivated to combine the method of Jacob et al. with the inclusion of detection of polymorphism in NE transporter gene because this limitation would improve analysis to a molecular level, which would result in a better assessment the causative factors in orthostatic intolerance in human subjects.

B. Claims 1, 3, 6-13, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stober et al. (Amer J Med Genet., Vol. 67, pp. 523-532, 1996) in view of Jacob et al. (Circulation, Vol. 99, pp. 1706-1712, 1999).

Stober et al. teach a method of claim 1, and 17, for screening for susceptibility to norepinephrine (NE) transport in human subjects wherein Stober et al. teach that the method comprises (a) obtaining a biological sample from the human subjects (see page 524, column 1, paragraph 1-2 of materials and methods); and detecting a polymorphism of a norepinephrine (NE) transporter in the biological sample from the subjects (see page 524, column 2, paragraphs 2-6) and detecting the presence of the polymorphism (page 525, column 2, paragraph 1) and analyzing the susceptibility of the subject to a sub-optimal NE transport (see page 526, column 2, paragraph 1 of results).

With regard to claims 3, Stober et al. also teach that the method comprises (i) biological sample comprising nucleic acid (see page 524, column 2, paragraph 2);

With regard to claim 6 Stober et al teach detection of polymorphism by amplifying the target nucleic acid using PCR (see page 524, column 2, paragraph 4);

With regard to claim 7, Stober et al. teach detection of the polymorphism using oligonucleotide primers (see page 525, table I)

With regard to claim 8, Stober et al. teach oligonucleotide primers hybridizes to exon 9 of NE transporter gene (see page 525, table I, page 526, table III).

With regard to claims 9-13, Stober et al. use of labeled primers with biotin and sequencing using dideoxy sequencing method (see page 525, column 1, lines 1-8).

Although Stober et al. teach assessing an association between the presence of a

polymorphism in NE transporter gene and NE transport, Stober et al. did not specifically teach the presence of a polymorphism in NET gene as an indication of the susceptibility of the subject to a sub-optimal norepineprine transport.

Jacob et al. teach a method of claim 2, for screening for susceptibility to sub-optimal nor epinephrine (NE) transport in human subjects with orthostatic intolerance wherein Jacob et al. teach that the method comprises (a) obtaining a biological sample from the subject having orthostatic intolerance (see page 1707, column 1, paragraph 1); and detecting sup-optimal norepinephrine (comprises protein) in the biological samples (see page 1707, column 2, paragraphs 1-4, page 1708, column 2, paragraph 2) and associating the presence of abnormal NE transport to the susceptibility of a subject to orthostatic intolerance or sub-optimal NE clearance (see page 1710, column 1, paragraphs 1-2, column 2, paragraph 1, page 1711, column 2, paragraph 3).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of detecting a polymorphism in NE transporter gene as taught by Stober et al. with determining abnormal norepinephrine clearance in orthostatic intolerance as taught by Jacob et al. to achieve expected advantage of developing a sensitive method for detecting susceptibility of a subject to sub-optimal NE transport because Jacob et al. taught that "impairment in the norepinephrine transporter could be responsible for the decreased norepinephrine spillover observed in the OI patients and the role of norepinephrine transporter function in the dramatic abnormalities in catecholamine clearance must receive increased attention" (see page 1710, column 2, paragraph 1, and page1711, column 2, paragraph 3). An ordinary practitioner would have been motivated to combine the method of

Stober et al. with incorporating the association of NE transport abnormality because this limitation would improve analysis, which in turn would result in a better detection of orthostatic intolerance in human subjects.

Response to arguments

7. The rejection made under 35 U.S.C. 112 second paragraph in the previous office action is withdrawn herein in view of the applicants' amendment (Paper No.11).

8. With reference to the rejections made under 35 USC 102(b), Applicant's arguments and have been fully considered. As pointed out by the Applicants, it is recognized that the prior art (Flattem et al) of the record is qualified as 102(a) reference, The declaration submitted by the applicants in anticipation of a rejection under 35 USC 102(a) is fully considered and the rejection is withdrawn in view of the arguments and the declaration.

9. The following is the rejection made in the previous office action under 35 USC 102(b):

Claims 1, 3, 6-7, 13, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Jonnsson et al. (Psychiatry Research, Vol. 79, pp. 1-9, 1998).

Jonnsson et al. teach a method for screening for susceptibility to norepinephrine (NE) transport in a human subject wherein Jonnsson et al. teach that the method comprises (a) obtaining a biological sample from a human subject (see page 3, column 1, paragraph 1); and detecting a polymorphism of a norepinephrine (NE) transporter in the biological sample from the subject (see page 3, column 2, paragraph 3) and detecting the presence of the polymorphism as an indication of the susceptibility of the subject to a sub-optimal NE transport (see page 7, column 1, paragraph 2). Jonnsson et al. also teach that the method comprises (i) biological sample comprising nucleic acid (see page 3, column 1, paragraph 2); (ii) detection of polymorphism by amplifying the target nucleic acid using PCR (see page 3, column 2, paragraph 3); (iii) detecting the polymorphism using a reagent (oligonucleotide primers) (see page 3, column 2, paragraph 3); and human subjects (see page 3, column 1, paragraph 1). Thus the disclosure of Jonnsson et al. meets the limitations in the instant claims.

Response to arguments:

Applicants' arguments with reference to the above rejection are fully considered and found persuasive in part. Applicants argue that Jonsson et al. reference does not teach a polymorphism in NE transporter gene, instead the reference teach a silent RFLP, meaning that the nucleic acid change G1287A does not result in any amino acid change in the NET polypeptide. The argument is fully considered and found not persuasive because Jonsson et al. does teach a polymorphism in NE transporter gene as discussed in the rejection above, however, the argument that mutation of G1287A shown by Jonsson et al. is a silent mutation meaning that the change in a single base of the nucleic acid doest not result in any amino acid change in NE transporter gene, is irrelevant to the instant context, because the instant claim 1 does not recite the limitation, that is, whether the polymorphism is a sense or missense or silent mutation. Further, Applicants argue that Jonsson et al. does not teach a relationship between the presence of the polymorphism and susceptibility to sub-optimal norepinephrine transport. This argument is fully considered and found persuasive because Jonsson et al. teach that the genotype variation in NE transporter gene may participate in differential regulation (comprises sub-optimal) norepinephrine turnover (see page 7, column 2, lines 5-9, page 1, abstract), and did not indicate the presence of polymorphism as an indication of the susceptibility of the subject to a suboptimal NE transport. Therefore the rejection is withdrawn in view of arguments and new grounds of rejections.

10. With reference to the rejections made in the previous office action under 103(a), Applicants' arguments and amendment are fully considered and the rejection is withdrawn in view of the arguments and new grounds of rejection (Paper No. 11).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
November 17, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER